Influenza-associated Aspergillosis in Critically Ill Patients

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Influenza-associated Aspergillosis in Critically Ill Patients

To the Editor:

Invasive aspergillosis is a well-known complication in immunocompromised patients but may also develop in patients with influenza pneumonia. The largest reported series included nine cases of invasive aspergillosis among 40 critically ill patients with influenza A H1N1 infection (23%) over a period of 3 years in two centers (1). Influenza-associated aspergillosis (IAA) may develop in immunocompromised patients (1, 2), but it has also been reported in apparently immunocompetent patients and was associated with the use of corticosteroids (1, 3, 4). Review of all 68 cases with IAA reported during the last 60 years indicated an overall mortality rate of 47% (5).

We conducted a multicenter retrospective observational study involving all eight academic tertiary care intensive care units (ICUs) in the Netherlands from December 2015 to April 2016, aimed at describing the diagnosis, treatment, and outcome of IAA in adults. All data were processed anonymously, and the ethics committee waived informed consent.

Influenza cases were identified both by reviewing all patients with a positive influenza polymerase chain reaction in the registry of the local microbiology department and matching these with ICU admission, and via using national ICU registrations of viral pneumonia and oseltamivir treatment to identify patients diagnosed with influenza or treated for influenza at a referring hospital. The IAA case definition included confirmed influenza diagnosis based on a positive result from a reverse transcriptase polymerase chain reaction test for influenza A and B from nasopharyngeal swab, sputum, or bronchoalveolar lavage (BAL) fluid. Furthermore, new infiltrates on the chest X-ray or computed tomography scan had to be present, as well as clinical symptoms including refractory fever or worsening of respiratory insufficiency despite more than 3 days of antibiotic therapy, dyspnea, hemoptysis, and/or pleural friction rub. Mycological evidence included histopathology or direct microscopic evidence of dichotomous branching hyphae with positive culture for Aspergillus from tissue. In addition, a galactomannan optical index in BAL of more than 1 or in bronchoalveolar lavage (BAL) fluid. Mycological evidence included histopathology or direct microscopic evidence of dichotomous branching hyphae with positive culture for Aspergillus from tissue. In addition, a galactomannan optical index in BAL of more than 1 or in bronchoalveolar lavage (BAL) fluid.

Review of all 68 cases with IAA reported during the last 60 years indicated an overall mortality rate of 47% (5).

We observed IAA in critically ill patients with influenza and identified 11 patients who were previously healthy (seven) or had no known risk for invasive aspergillosis (four). The mortality rate of IAA was high; it was higher than the previously reported 47% mortality rate (5). The mortality rate among patients without risk factors was not lower compared with those with low, intermediate, or high risk for invasive fungal disease. Delayed diagnosis of IAA in the ICU and subsequent delayed antifungal therapy might have contributed to this high mortality. The clinical presentation of IAA differed substantially from presentations seen in patients with classic risk factors. The observation of two patients with Aspergillus tracheobronchitis underscores the need to further characterize clinical and radiological features of IAA (8). Furthermore, a high triazole resistance frequency was observed, which appears to be higher in the Netherlands than in other countries and further compromises successful patient management (9).

It is important to understand the pathogenesis of IAA from the perspective of virus, fungus, and host. Strikingly, in line with our observation, almost all cases to date have been associated with the pandemic influenza A H1N1 infection. Although it has been shown that early treatment with antiviral drugs in influenza reduces mortality, especially in adults (10), we observed a very high mortality of 61%, despite antiviral therapy. Whether influenza A H1N1 has unique properties that predispose to IAA remains to be investigated.

In a previous study, corticosteroid treatment was suggested to be the main risk factor for developing IAA in the ICU (1). Although 18 of 23 patients received steroids, our cohort also included 5 patients who did not receive corticosteroids, and 2 of them had no underlying condition. This suggests that corticosteroids might not be the only predisposing factor contributing to IAA.

Our study indicates that increased awareness of IAA as an early complication of influenza, prompt diagnoses, and initiation...
Table 1. Underlying Disease, Influenza Type, *Aspergillus* Diagnosis, Initial Antifungal Therapy, and Outcome of 23 Patients with Influenza-associated Aspergillosis

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Sex/Age (yr)</th>
<th>Underlying Disease</th>
<th>Influenza Type</th>
<th>BAL GMI</th>
<th>Serum GMI</th>
<th>BAL Culture</th>
<th>In Vitro Susceptibility*</th>
<th>Corticosteroids</th>
<th>Initial Antifungal Therapy</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-1</td>
<td>F/34</td>
<td>None</td>
<td>A, H1N1</td>
<td></td>
<td>5.3</td>
<td></td>
<td>Wild-type and azole resistant</td>
<td>No</td>
<td>Voriconazole</td>
<td>Died (+27)</td>
</tr>
<tr>
<td>3-1</td>
<td>M/63</td>
<td>Hypertension, arthrosis</td>
<td>A, NT</td>
<td>1.5</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole + Lip-AmB</td>
<td>Died (+38)</td>
</tr>
<tr>
<td>3-3</td>
<td>M/65</td>
<td>FSGS</td>
<td>A, NT</td>
<td>6.5</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>No</td>
<td>Voriconazole</td>
<td>Died (+21)</td>
</tr>
<tr>
<td>4-2</td>
<td>M/52</td>
<td>None</td>
<td>A, H1N1</td>
<td>13.6</td>
<td></td>
<td>A. fumigatus</td>
<td>Azole resistant</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+13)</td>
</tr>
<tr>
<td>4-3</td>
<td>M/62</td>
<td>Churg-Strauss syndrome</td>
<td>A, NT</td>
<td>4.5</td>
<td>0.2</td>
<td>Negative</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+12)</td>
</tr>
<tr>
<td>4-4</td>
<td>F/61</td>
<td>Kidney transplant</td>
<td>A, NT</td>
<td>11.7</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+7)</td>
</tr>
<tr>
<td>5-3</td>
<td>M/62</td>
<td>None</td>
<td>A, NT</td>
<td>2.4</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type and azole resistant</td>
<td>Yes</td>
<td>Voriconazole + anidulafungin</td>
<td>Died (+11)</td>
</tr>
<tr>
<td>5-4</td>
<td>M/67</td>
<td>GPA</td>
<td>A, H1N1</td>
<td>8.3</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole + anidulafungin</td>
<td>Died (+8)</td>
</tr>
<tr>
<td>5-5</td>
<td>F/38</td>
<td>None</td>
<td>A, H1N1</td>
<td>2.0</td>
<td>0.9</td>
<td>A. fumigatus</td>
<td>Wild-type and azole resistant</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+16)</td>
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<tr>
<td>5-6</td>
<td>M/53</td>
<td>None</td>
<td>A, NT</td>
<td>7.4</td>
<td>0.1</td>
<td>Negative</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole + caspofungin</td>
<td>Died (+43)</td>
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<tr>
<td>7-1</td>
<td>F/60</td>
<td>COPD</td>
<td>A, NT</td>
<td>2.8</td>
<td></td>
<td></td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+31)</td>
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<tr>
<td>7-2</td>
<td>F/67</td>
<td>Nonmalignant hematological disease</td>
<td>A, H1N1</td>
<td>2.8</td>
<td>0.1</td>
<td>Negative</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+25)</td>
</tr>
<tr>
<td>7-3</td>
<td>M/66</td>
<td>GPA</td>
<td>A, H1N1</td>
<td>6.2</td>
<td>0.1</td>
<td>Negative</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Died (+27)</td>
</tr>
<tr>
<td>7-5</td>
<td>F/80</td>
<td>Churg-Strauss syndrome</td>
<td>A, H1N1</td>
<td>1.2</td>
<td></td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Lip-AmB</td>
<td>Died (+17)</td>
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<tr>
<td>2-2</td>
<td>F/53</td>
<td>Hematologic malignancy</td>
<td>A, H1N1</td>
<td>2.9</td>
<td>0.6</td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
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<tr>
<td>2-3</td>
<td>F/45</td>
<td>Asthma, sinusitis</td>
<td>B</td>
<td>8.6</td>
<td>0.6</td>
<td>A. fumigatus</td>
<td>Wild-type and azole resistant</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>4-1</td>
<td>M/64</td>
<td>None</td>
<td>A, H1N1</td>
<td>10.4</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>5-2</td>
<td>M/50</td>
<td>COPD</td>
<td>B</td>
<td>0.6</td>
<td></td>
<td>Wild-type</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>1-1</td>
<td>M/64</td>
<td>Myelofibrosis</td>
<td>A, NT</td>
<td>11.7</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>No</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>6-1</td>
<td>M/70</td>
<td>Hematologic malignancy</td>
<td>A, H1N1</td>
<td>0.1</td>
<td>4.2</td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
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<tr>
<td>6-2</td>
<td>M/57</td>
<td>Cystic fibrosis</td>
<td>A, H1N1</td>
<td>1.5</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>Yes</td>
<td>Voriconazole</td>
<td>Survived</td>
</tr>
<tr>
<td>6-3</td>
<td>M/55</td>
<td>None</td>
<td>A, H1N1</td>
<td>2.8</td>
<td></td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>No</td>
<td>Voriconazole + micafungin</td>
<td>Survived</td>
</tr>
<tr>
<td>7-4</td>
<td>M/65</td>
<td>Kidney transplant</td>
<td>A, NT</td>
<td>1.4</td>
<td>0.6</td>
<td>A. fumigatus</td>
<td>Wild-type</td>
<td>No</td>
<td>Voriconazole + micafungin</td>
<td>Survived</td>
</tr>
</tbody>
</table>

Definition of abbreviations: *A. fumigatus* = *Aspergillus fumigatus*; BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; FSGS = focal segmental glomerulosclerosis; GMI = galactomannan index; GPA = granulomatosis with polyangiitis; ID = identification number; Lip-AmB = lipid formulation of amphotericin B; NT = not typed.

*In three patients, wild-type and azole-resistant *A. fumigatus* colonies were recovered from culture.

†Parentheses show number of days from diagnosis of influenza.
of appropriate antifungal therapy might prove to be important to decrease mortality of influenza in coming seasons.

**Author disclosures** are available with the text of this letter at www.atsjournals.org.

Frank L. van de Veerdonk, Ph.D., M.D.
Eva Kolwijck, Ph.D., M.D.
Radboud University Medical Centre
Nijmegen, the Netherlands

Caspar J. Hodiamont, Ph.D., M.D.
Academic Medical Centre
Amsterdam, the Netherlands

Bart J. A. Rijnders, Ph.D., M.D.
Erasmus Medical Centre
Rotterdam, the Netherlands

Judith van Paassen, M.D.
Leiden University Medical Centre
Leiden, the Netherlands

Pieter-Jan Haas, Ph.D., M.D.
University Medical Centre
Utrecht, the Netherlands

Claudy Oliveira dos Santos, M.D.
Greetje A. Kampinga, Ph.D., M.D.
University Medical Centre Groningen
Groningen, the Netherlands

Dennis C. J. J. Bergmans, Ph.D., M.D.
Maastricht University Medical Centre
Maastricht, the Netherlands

Karin van Dijk, Ph.D., M.D.
VU University Medical Centre
Amsterdam, the Netherlands

Anton F. J. de Haan, M.Sc.
Radboud University Medical Centre
Nijmegen, the Netherlands

Jaap van Dissel, Ph.D., M.D.
National Institute of Public Health and the Environment
Bilthoven, the Netherlands

Hans G. van der Hoeven, Ph.D., M.D.
Paul E. Verweij, Ph.D., M.D.
Radboud University Medical Centre
Nijmegen, the Netherlands

Dutch-Belgian Mucosis Study Group*

*The Dutch-Belgian Mucosis Study Group includes the following participants: Janette C. Rahamat-Langendoen, Bart-Jan Kullberg, Mihai G. Netea, Roger J. Bruggeman, Astrid W. Hoedemaekers, and Willem J. G. Meiners (Radboud University Medical Centre, Nijmegen); Wieke Freudenburg, Nienke Roescher, W. Joost Wiersinga, and Charlotte H. S. B. van den Berg (Academic Medical Centre, Amsterdam); Alieke G. Vonk, Carla van Tienen, and Ben van der Hoven (Erasmus Medical Centre, Rotterdam); Martha T. van der Beek (Leiden University Medical Centre, Leiden); Lennie P.G. Derde (University Medical Centre Utrecht, Utrecht); Coretta van Leer and Heleen Aardema (University Medical Centre Groningen, Groningen); Astrid Oude Lashof (Maastricht University Medical Centre, Maastricht); and C. Wim Ang (VU University Medical Centre, Amsterdam).

**References**


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Vascular Stiffness and Mechanotransduction: Back in the Limelight

To the Editor:

Decades of extensive research in the field of pulmonary hypertension (PH) have led to the discovery of several pathogenic drivers and, thus, targeting possibilities. Despite that, there remains a lack of effective therapeutic options with major vasodilatation therapies that have a limited influence on vascular remodeling (1). Vascular remodeling, characterized by medial wall thickening, plexiform lesions, and intimal hyperplasia, is an outcome of excessive proliferation, migration, and survival of pulmonary artery smooth muscle cells (PASMCs), endothelial cells, and fibroblasts (2). This therapeutic deficit demonstrates a need for intensive investigation of the detailed mechanisms underlying vasodilation and vascular remodeling and, preferably, determining a link between them to target them together. Although vascular stiffening associated with aberrant collagen and elastin deposition in the extracellular matrix (ECM) at end-stage PH has been long recognized (3), emerging evidence also supports the idea that stiffening can precede the development of PH and promotes pulmonary vascular remodeling (4, 5). Vascular stiffening in the proximal and distal pulmonary arterial tree occurs in various forms of PH (3, 6), and stiffness is an index of disease progression (7). Furthermore, recent studies demonstrate that pulmonary vascular (PV) stiffness has significant prognostic value in PH. PV stiffness correlates with mortality in patients with PH, and moreover, measurements of PV stiffness are considered to be more accurate in assessing right ventricular afterload and may even be superior to PV resistance in predicting mortality (8, 9). These observations raise the possibility that PV stiffness is a critical factor that must be treated to improve outcomes for patients with PH.

However, the exact role of vascular stiffening in the development and progression of PH has yet to be defined. In particular, the field has lacked a clear understanding of the spatiotemporal development of PV stiffness and what distinct responses to proximal versus distal PV stiffening contribute to PH pathogenesis and progression. In addition, although it is becoming increasingly clear that measurement of changes in PV stiffness/arterial flow pulse waves are likely to be incorporated into medical practice for diagnosis or prognosis of PH, many remain skeptical that vascular stiffness is a desirable treatment target. A major contributor to this skepticism is the lack of studies delineating a causal relationship between artery stiffness and PH progression. An essential question that further arises is what exactly leads to an increase in distal vascular stiffness in response to pathological stimuli. In parallel, we do not know how early changes in the local mechanical environment contribute to progressive vascular remodeling and promote the development of PH. What are the mechanosensitive pathways/factors that are activated, and how can they regulate cellular proliferation, survival, metabolism, and the ECM, particularly during the development and progression of PH?

Three recent and independent studies shed light on these important issues. Together, Liu and colleagues (5) and Bertero and colleagues (10) suggest that vascular stiffness–induced mechanical stress is sufficient to activate cellular pathways in vascular cells, leading to enhanced proliferation, migration, and matrix deposition. These changes can, in turn, further perpetuate vascular stiffening, giving rise to a self-sustainable loop amplifying vascular remodeling in PH. Ruffenach and colleagues (11) provide strong support in favor of microRNA(miR)-204/Runt-related transcription factor 2 (RUNX2)/hypoxia-inducible factor-1α axis as a driver of stiffness via promoting vascular calcification in distal vasculature (Figure 1).

Human PH patients and animal models for PH, such as hypoxic calves, rats, and mice, are all characterized by increased stiffness or reduced compliance of pulmonary arteries (PAs) and/or right ventricular dysfunction. This strongly suggested a causative role of vascular stiffening in the pathogenesis of PH. These findings were supported by a significant increase in small vessel stiffness observed in patients with idiopathic pulmonary arterial hypertension. Further cementing this role, the authors showed that matrix stiffening directly activated the proliferation of PASMCs and pulmonary artery endothelial cells and triggered PASMCs to produce ECM and exaggerated traction forces. On the basis of their